Impact of Mitral Regurgitation on Clinical Outcomes of Patients With Low-Ejection Fraction, Low-Gradient Severe Aortic Stenosis Undergoing Transcatheter Aortic Valve Implantation

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Background—Up to 1 in 6 patients undergoing transcatheter aortic valve implantation (TAVI) present with low-ejection fraction, low-gradient (LEF-LG) severe aortic stenosis and concomitant relevant mitral regurgitation (MR) is present in 30% to 55% of these patients. The effect of MR on clinical outcomes of LEF-LG patients undergoing TAVI is unknown.

Methods and Results—Of 606 consecutive patients undergoing TAVI, 113 (18.7%) patients with LEF-LG severe aortic stenosis (mean gradient ≤40 mm Hg, aortic valve area <1.0 cm^2, left ventricular ejection fraction <50%) were analyzed. LEF-LG patients were dichotomized into ≤mild MR (n=52) and ≥moderate MR (n=61). Primary end point was all-cause mortality at 1 year. No differences in mortality were observed at 30 days (*P*=0.76). At 1 year, LEF-LG patients with ≥moderate MR had an adjusted 3-fold higher rate of all-cause mortality (11.5% versus 38.1%; adjusted hazard ratio, 3.27 [95% confidence interval, 1.31–8.15]; *P*=0.011), as compared with LEF-LG patients with ≤mild MR. Mortality was mainly driven by cardiac death (adjusted hazard ratio, 4.62; *P*=0.005). As compared with LEF-LG patients with ≥moderate MR assigned to medical therapy, LEF-LG patients with ≥moderate MR undergoing TAVI had significantly lower all-cause mortality (hazard ratio, 0.38; 95% confidence interval, 0.019–0.75) at 1 year.

Conclusions—Moderate or severe MR is a strong independent predictor of late mortality in LEF-LG patients undergoing TAVI. However, LEF-LG patients assigned to medical therapy have a dismal prognosis independent of MR severity suggesting that TAVI should not be withheld from symptomatic patients with LEF-LG severe aortic stenosis even in the presence of moderate or severe MR. **(*Circ Cardiovasc Interv*. 2015;8:e001895. DOI: 10.1161/CIRCINTERVENTIONS.114.001895.)**

Key Words: aortic valve stenosis ■ mitral valve insufficiency ■ transcatheter aortic valve implantation

The combination of a low left ventricular ejection fraction (LVEF) with a tight aortic orifice is frequently associated with a low transvalvular pressure gradient among patients with severe aortic stenosis (AS).[1–9] Low-ejection fraction, low-gradient severe AS (LEF-LG), represents a management challenge because of the high perioperative risk associated with conventional surgical aortic valve replacement (SAVR).[1,2,6,10,11] Transcatheter aortic valve implantation (TAVI) is a less invasive alternative procedure to SAVR for the treatment of high-risk patients presenting with symptomatic severe AS.[12,13] Several studies have demonstrated the feasibility of TAVI to treat patients with symptomatic LEF-LG severe AS,[7,9,14–17] which is reflected in the recent 2014 American Heart Association/American College of Cardiology guidelines providing a class IIa recommendation for TAVI for the treatment of symptomatic LEF-LG in high-risk patients.[18]

LEF-LG is present in ≈5% to 10% of the overall population of patients with severe AS.[6] However, the prevalence of LEF-LG among patients undergoing TAVI is higher (10% to 16%) because of the predominance of high-risk patients.[7,9,14,15] Moderate to severe mitral regurgitation (MR) is present in 2% to 22% of unselected patients undergoing TAVI,[19–22] whereas its prevalence in LEF-LG patients undergoing TAVI is considerably higher (20% to 55%).[7,9,14,15] Recently, several conflicting

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WHAT IS KNOWN

- Low-ejection fraction, low-gradient (LEF-LG) severe aortic stenosis is associated with a high perioperative mortality after conventional surgical aortic valve replacement but is associated with a dismal prognosis with conservative management.
- Evidence, to date, on the effect of mitral regurgitation (MR) on clinical outcomes of unselected patients after transcatheter aortic valve implantation has been conflicting.
- Transcatheter aortic valve implantation has been shown to be a viable alternative to conventional surgical aortic valve replacement for the treatment of patients with LEF-LG severe aortic stenosis, although overall and cardiovascular mortality rates remain stubbornly high.

WHAT THE STUDY ADDS

- Despite a similar baseline risk profile, LEF-LG patients with ≥moderate MR had an adjusted 3-fold higher rate of overall mortality at 1 year as compared with similar patients with mild or less MR.
- Among patients with ≥moderate MR, those with degenerative MR had the worst prognosis.
- When compared with unmatched control LEF-LG severe aortic stenosis patients with ≥moderate MR assigned to medical therapy during the same treatment period, LEF-LG severe aortic stenosis patients with ≥moderate MR undergoing transcatheter aortic valve implantation had significantly better outcomes suggesting that transcatheter aortic valve implantation should not be withheld from such patients.

studies reporting the effect of MR on clinical outcomes among unselected patients undergoing TAVI have emerged.[23–29] However, to date, no data exist on whether MR affects clinical outcomes among selective patients with LEF-LG undergoing TAVI. Therefore, the primary aim of this study was to assess the association of MR with clinical outcomes among this high-risk–selected patient population undergoing TAVI. The secondary aim was to compare clinical outcomes of LEF-LG patients assigned to TAVI versus a control medical therapy (MT) group stratified according to MR grade.

Methods

Patient Population

Since 2007, patients with severe AS and increased surgical risk underwent a multidisciplinary assessment and were assigned to 1 of 3 treatment modalities that is, MT, conventional SAVR, or TAVI. During the period between August 2007 and December 2012, 606 patients were assigned to TAVI and 110 patients were assigned to MT.[30] One hundred thirteen consecutive patients with symptomatic, severe LEF-LG native valve AS undergoing TAVI were included in this study (n=113/606; 18.6%; aortic valve area <1.0 cm2, mean gradient ≤40 mm Hg, and LVEF <50%). Of the 110 consecutive patients assigned to MT, 44 patients had symptomatic LEF-LG severe AS, as previously described.[30] Included patients with LEF-LG severe AS were dichotomized based on the presence of mild or less MR or moderate or severe MR at baseline echocardiographic examination. This study complies with the Declaration of Helsinki, was approved by the local ethics committee, and all patients provided informed written consent.

Echocardiography

Transthoracic echocardiography was performed in all included patients at baseline as described in detail in the Data Supplement.

Dobutamine Stress Echocardiography

Dobutamine stress echocardiography was performed in one third of TAVI patients (n=36/113 [32%]) and in 5/39 (13%) MT patients as described in the Data Supplement.

Cardiac Catheterization

All TAVI patients underwent coronary angiography and 89 of 113 (79%) TAVI patients had a full invasive hemodynamic evaluation by right and left heart catheterization before TAVI as previously described.[9] Twenty-nine of thirty-nine patients assigned to MT underwent coronary angiography of which 27 patients had a simultaneous right heart catheterization. Pulmonary hypertension was defined as an invasive mean PA pressure >25 mm Hg and was dichotomized into precapillary (left ventricular end-diastolic pressure ≤15 mm Hg) and postcapillary (left ventricular end-diastolic pressure >15 mm Hg) subgroups.

Transcatheter Aortic Valve Implantation

TAVI was performed as previously described.[31] Vascular access was transfemoral using the Edwards Sapien/XT valve (Edwards Lifesciences, Irvine, CA) or the Medtronic CoreValve Revalveing System (Medtronic Inc, Minneapolis, MN, transapical for the Edwards Sapien/XT valve or self-expanding Symetis Acurate TA valve (Symetis Inc, Switzerland) or transsubclavian using the Medtronic CoreValve Revalveing System.

Clinical Follow-Up

Adverse events were assessed in hospital, and regular clinical follow-up was performed at 1, 6, and 12 months by means of a clinical visit or standardized telephone interview. All suspected events were adjudicated by an unblinded clinical event committee. Baseline clinical and procedural characteristics and all follow-up data were entered into a dedicated database, held at an academic clinical trials unit (CTU Bern, Bern University Hospital, Switzerland) responsible for central data audits and maintenance of the database.

Study End Points

Clinical end points were defined according to the criteria proposed by the Valve Academic Research Consortium-2 consensus document.[32] Primary end point was all-cause mortality at 1 year. Secondary end points included all-cause mortality at 30 days and cardiovascular death, and major adverse cardiovascular and cerebrovascular events (composite of all-cause mortality, major stroke, and myocardial infarction) at 30 days and 1 year. New York Heart Association (NYHA) functional class status was assessed at baseline and 1-year follow-up. Transthoracic echocardiography was performed during follow-up. Transthoracic echocardiography performed on patients who survived to discharge and 1 year, respectively, are included in this analysis.

Statistics

Continuous data are presented as mean±SD, and categorical variables are depicted as percentages and numbers. Categorical variables were compared by means of the χ^2 test (or Fisher test for 2 group comparisons), and continuous variables were compared using the unpaired *t* test. NYHA functional status at 1 year was

Table 1. Baseline Characteristics

	TAVI Patients		
	Mild or Less MR	Moderate or Severe MR	
	n=52	n=61	*P* Value
Age, y	82.2±4.9	82.0±5.2	0.81
Women, n (%)	14 (26.9)	32 (52.5)	0.010
Height, cm	167.2±7.0	164.0±8.4	0.031
Weight, kg	73.5±13.9	66.2±13.9	0.006
Body mass index, kg/m^2	26.3±4.5	24.6±5.0	0.06
Body surface area, m^2	1.8±0.2	1.71±0.2	0.003
Cardiac risk factors			
Diabetes mellitus, n (%)	18 (34.6)	21 (34.4)	0.98
Hypercholesterolemia, n (%)	39 (75.0)	37 (60.7)	0.11
Hypertension, n (%)	44 (84.6)	47 (77.0)	0.31
Current smoker, n (%)	7 (13.5)	6 (9.8)	0.55
Past medical history			
Previous stroke, n (%)	6 (11.5)	7 (11.5)	0.99
Peripheral vascular disease, n (%)	11 (21.2)	20 (32.8)	0.24
Chronic obstructive pulmonary disease, n (%)	10 (19.6)	8 (13.1)	0.35
Renal failure (GFR<50 mL/min per 1.73 m^2)	14 (26.9)	25 (41.0)	0.12
Previous permanent pacemaker, n (%)	6 (11.5)	8 (13.1)	0.80
Coronary artery disease, n (%)	37 (71.2)	47 (77.0)	0.62
Previous MI, n (%)	15 (28.8)	16 (26.2)	0.92
Previous CABG, n (%)	13 (25.0)	17 (27.9)	0.90
Previous PCI, n (%)	22 (42.3)	22 (36.1)	0.50
Atrial fibrillation, n (%)	11 (21.6)	15 (25.0)	0.67
Symptoms			
New York Heart Association (NYHA) Functional Class			
NYHA III/IV, n (%)	37 (71.2)	51 (83.6)	0.11
CCS angina status			
CCS III/IV, n (%)	9 (17.3)	7 (11.5)	0.38
Risk assessment			
Logistic EuroScore, %	32.9±14.1	35.5±16.4	0.37
STS score, %	7.1±4.4	8.67±5.0	0.08
Medications at baseline			
Diuretic, n (%)	35 (67.3)	50 (82.0)	0.07
β-blocker, n (%)	30 (57.7)	39 (63.9)	0.50
ACEi/ARB, n (%)	29 (55.8)	38 (62.3)	0.48
Statin, n (%)	31 (59.6)	30 (49.2)	0.27
Laboratory values			
B-type natriuretic peptide, pg/mL	1065±943	1164±1078	0.69

Values are n (%) or mean±SD with *P* values from unpaired *t* tests or counts (%) with *P* values from χ^2 tests. ACEi indicates angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; CABG, coronary artery bypass grafting; CCS, Canadian Cardiovascular Society; MR, mitral regurgitation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; and TAVI, transcatheter aortic valve implantation.

analyzed using χ^2 tests. Time-to-event data are presented using Kaplan–Meier curves, with incidence rates calculated from life-tables, at 30 days and 1-year follow-up, respectively, for patients undergoing TAVI and 1-year follow-up for comparisons between MT and TAVI patients. Univariate and adjusted Cox proportional hazard models were used to derive hazard ratio (HR) estimates of clinical time-to-event comparisons between the 2 groups. Twenty-three baseline variables were added into the univariate model. In the adjusted Cox models, only peripheral vascular disease (P=0.003) and the logistic EuroSCORE (P<0.001) were added because these were the only 2 factors with a P<0.1 affecting major adverse cardiovascular and cerebrovascular events. Baseline, discharge to 1-year follow-up changes in echocardiographic parameters were analyzed using linear mixed models with a random effect of the patient identifier to account for repeated measures per patient. Only survivors at discharge or at 1-year follow-up, respectively, were included in these repeated measures analyses. All P values and 95% confidence intervals (CIs) are 2-sided. Two-sided P<0.05 were considered

Table 2. Baseline Echocardiographic Characteristics

	TAVI Patients		
	Mild or Less MR	Moderate or Severe MR	
	n=52	n=61	*P* Value
Aortic stenosis severity			
Aortic valve area, cm^2	0.74±0.23	0.73±0.200	0.93
Indexed aortic valve area, cm^2/m^2	0.41±0.12	0.43±0.12	0.30
Aortic maximal velocity, cm/s	3.3±0.7	3.2±0.5	0.30
Mean gradient, mm Hg	29.6±10.1	27.5±10.5	0.29
Peak gradient, mm Hg	47.3±16.5	45.8±15.6	0.65
LV geometry and two-dimensional measurements			
Interventricular septum in diastole, cm	1.4±0.3	1.2±0.3	0.024
Posterior wall thickness in diastole, cm	1.4±0.9	1.1±0.2	0.11
LV end-systolic diameter, cm	4.4±0.9	4.5±1.3	0.58
LV end-diastolic diameter, cm	5.6±9.1	5.5±1.2	0.44
Relative wall thickness	0.5±0.4	0.5±0.4	0.72
LV mass index, g/m^2	161.6±39.2	158.6±33.5	0.74
Normal geometry, n (%)	1 (3.8)	2 (6.5)	0.51
Concentric hypertrophy, n (%)	10 (38.5)	16 (51.6)	0.51
Eccentric hypertrophy, n (%)	12 (46.2)	12 (38.7)	0.51
Concentric remodeling, n (%)	3 (11.5)	1 (3.2)	0.51
LV systolic function			
LV ejection fraction, %	36.1±9.7	32.7±12.4	0.11
LVOT diameter, mm	21.4±2.0	20.3±2.7	0.14
Stroke volume, mL	59.7±18.1	48.8±17.2	0.057
Stroke volume index, mL/m^2	33.4±10.8	28.7±9.7	0.16
LV diastolic function			
E/A ratio	1.7±1.3	2.1±0.9	0.25
Deceleration time, ms	199.2±79.2	144.7±27.4	0.009
Isovolumic relaxation time, ms	80.5±31.4	80.9±38.4	0.99
Left atrial diameter, mm	48.3±7.1	50.1±5.1	0.26
RV systolic function			
Tricuspid annular plane systolic excursion, cm	1.4±0.4	1.5±0.5	0.60
Pulse doppler peak velocity at the annulus, cm/s	9.5±3.0	9.5±3.0	0.99
RV dimensions			
RV dilatation, n (%)	9 (19.1)	11 (21.2)	0.80
Associated valvular abnormality			
Aortic regurgitation			0.50
None/trivial, n (%)	12 (25.0)	17 (30.9)	
Mild, n (%)	33 (68.8)	32 (58.2)	
Moderate, n (%)	3 (6.3)	6 (10.9)	
Severe, n (%)	0 (0)	0 (0)	
MR			<0.0001
None/trivial, n (%)	2 (3.8)	0 (0)	
Mild, n (%)	50 (96.2)	0 (0)	
Moderate, n (%)	0 (0)	58 (95.1)	
Severe, n (%)	0 (0)	3 (4.9)	
EROA, mm^2	12.50±5.96	24.67±19.80	
Regurgitant volume, mL	16.25±4.03	41.14±32.05	
Tricuspid regurgitation			<0.0001
None/trivial, n (%)	9 (17.3)	2 (3.3)	
Mild, n (%)	37 (71.2)	30 (49.2)	
Moderate, n (%)	5 (9.6)	24 (39.3)	
Severe, n (%)	1 (1.9)	5 (8.2)	
Right-sided hemodynamics			
RV/RA gradient, mm Hg	39.9±11.6	43.5±12.1	0.20
Pulmonary artery systolic pressure, mm Hg	50.2±13.8	53.6±13.9	0.27

Values are n (%) or mean±SD. EROA indicates effective regurgitant orifice area; LV, left ventricle; LVOT, left ventricular outflow tract; MR, mitral regurgitation; RA, right atrium; RV, right ventricle; and TAVI, transcatheter aortic valve implantation.

Table 3. Invasive Hemodynamic Characteristics

	TAVI Patients		
	Mild or Less MR	Moderate or Severe MR	
	n=43	n=46	*P* Value
Aortic stenosis severity			
Aortic valve area, cm^2	0.69±0.25	0.66±0.33	0.63
Indexed aortic valve area, cm^2/m^2	0.38±0.15	0.38±0.20	0.96
Peak-to-peak gradient, mm Hg	31.5±22.2	31.4±20.0	0.98
Mean gradient, mm Hg	26.2±7.8	25.3±9.3	0.61
Stroke work loss, %	17.4±5.6	17.4±6.2	0.96
Systolic ejection period, s/min	23.37±5.3	23.8±4.6	0.67
Valvular resistance, dyne s/cm^5	183.7±93.8	232.5±129.5	0.048
Systemic vascular load			
Systolic arterial pressure, mm Hg	127.4±26.3	124.2±23.9	0.56
Diastolic arterial pressure, mm Hg	66.8±14.0	65.9±14.6	0.77
Mean arterial pressure, mm Hg	91.7±17.7	89.5±14.7	0.53
Systemic vascular resistance, mm Hg min/L	1973±643	2222±798	0.11
Systemic arterial compliance, mL/mm Hg	0.50±0.27	0.42±0.22	0.12
LV global afterload			
Valvuloarterial Impedance, mm Hg/mL per m^2	6.3±2.3	7.6±2.5	0.016
LV systolic function			
Ejection fraction,* %	33.7±8.7	30.7±8.2	0.10
LV systolic pressure, mm Hg	158.7±26.0	153.5±22.8	0.32
LV end-diastolic pressure, mm Hg	22.0±8.0	21.9±7.8	0.97
LV stroke work, g/m	78.4±25.2	59.2±19.9	<0.001
Stroke volume, mL	48.9±13.4	38.5±12.6	<0.001
Stroke volume index, mL/m^2	27.1±6.9	22.0±6.6	0.001
Cardiac output, L/min	3.7±1.1	3.1±0.9	0.013
Cardiac index, L/min per m^2	2.0±0.5	1.8±0.4	0.021
Heart rate, bpm^{-1}	75.1±11.9	84.3±18.6	0.008
Right-sided hemodynamics			
PA systolic pressure, mm Hg	54.1±15.6	62.5±12.9	0.009
Mean PA pressure, mm Hg	36.4±11.4	40.7±8.4	0.050
Pulmonary hypertension, n (%)	31 (72.1)	43 (93.5)	0.010
Precapillary PH, n (%)	3 (7.0)	9 (19.6)	0.013
Postcapillary PH, n (%)	28 (65.1)	34 (73.9)	
RA mean pressure, mm Hg	9.2±5.6	9.9±5.9	0.59
Components of Fick equation			
Aortic saturation, %	94.4±2.3	94.7±2.9	0.63
Pulmonary artery saturation, %	58.8±7.6	55.0±9.1	0.038
Hemoglobin, g/dL	12.7±1.8	12.1±1.6	0.11

Values are n (%) or mean±SD. Pulmonary hypertension defined as a mean PA pressure ≥25 mm Hg. LV indicates left ventricle; MR, mitral regurgitation; PA, pulmonary artery; PH, pulmonary hypertension; RA, right atrium; and TAVI, transcatheter aortic valve implantation.
*Angiographic ejection fraction.

statistically significant. All analyses were performed with STATA (version 12, StataCorp, College Station, TX).

Results

Of the 113 patients with LEF-LG severe AS undergoing TAVI in this study, 52 patients had mild or less MR and 61 patients had moderate or severe MR (58 moderate and 3 severe MR). Of 44 patients with LEF-LG assigned to MT, 5 were excluded (3 missing MR grade and 2 crossed over to TAVI during inclusion period and were included in the TAVI group). Of the 39 remaining MT patients, 19 had mild or less MR and 20 had moderate or severe MR. Baseline characteristics of TAVI patients stratified by MR grade are given in Table 1. Mean age was 82.1±5.0 years and there were significantly more women in the moderate or severe MR group. As a result, patients in the latter group were smaller and weighed less. No significant

Table 4. Procedural Characteristics

	TAVI Patients		
	Mild or Less MR	Moderate or Severe MR	
	n=52	n=61	*P* Value
General anesthesia, n (%)	23 (44.2)	23 (37.7)	0.48
Procedural duration, min	67±29	66±45	0.9
Aortic valve intervention			
Balloon predilation, n (%)	45 (86.5)	58 (95.1)	0.21
Medtronic CoreValve, n (%)	32 (49.2)	33 (54.1)	0.54
Edwards Sapien valve, n (%)	19 (36.5)	27 (44.3)	0.52
Symetis valve, n (%)	1 (1.9)	1 (1.6)	0.91
Vascular access			
Transfemoral, n (%)	38 (73.1)	47 (77.0)	0.79
Transapical, n (%)	11 (21.2)	12 (19.7)	
Transsubclavian, n (%)	3 (5.8)	2 (3.3)	
Revascularization, n (%)	18 (34.6)	22 (36.1)	0.87
Complete revascularization, n (%)	7 (13.5)	2 (3.3)	0.044
Vessels treated			
LM, n (%)	1 (2.5)	4 (10.0)	0.47
LAD, n (%)	12 (30.0)	11 (27.5)	0.46
LCX, n (%)	3 (7.7)	4 (10.3)	0.97
RCA, n (%)	9 (22.5)	3 (7.5)	0.032
Vein graft, n (%)	1 (2.7)	3 (8.1)	0.81
Concomitant PCI, n (%)	6 (11.5)	10 (16.4)	0.46
Staged PCI, n (%)	12 (23.1)	12 (19.7)	0.66
Hospital stay, d	7.7±3.3	8.0±7.1	0.74
Conversion to SAVR, n (%)	0 (0)	1 (1.6)	0.54
Postprocedural aortic regurgitation ≥2+, n (%)	10 (19.2)	9 (14.8)	0.37

Values are n (%) or mean±SD. LAD indicates left anterior descending; LCX, left circumflex; LM, left main stem; MR, mitral regurgitation; PCI, percutaneous coronary intervention; RCA, right coronary artery; SAVR, surgical aortic valve replacement; and TAVI, transcatheter aortic valve implantation.

differences in other baseline characteristics, including surgical risk scores, were observed between TAVI groups.

As compared with LEF-LG patients assigned to MT, patients undergoing TAVI had a lower prevalence of renal failure and atrial fibrillation, a higher prevalence of previous percutaneous coronary intervention and had lower surgical risk scores (Logistic EuroSCORE: 42.8±15.8% versus 34.3±15.4%; *P*=0.004; STS score: 11.3±7.2% versus 7.9±4.8%; *P*=0.001; Table I in the Data Supplement).

Baseline Echocardiographic Characteristics

Echocardiographic characteristics of TAVI patients stratified according to MR grade are presented in Table 2. No significant differences in baseline aortic valve

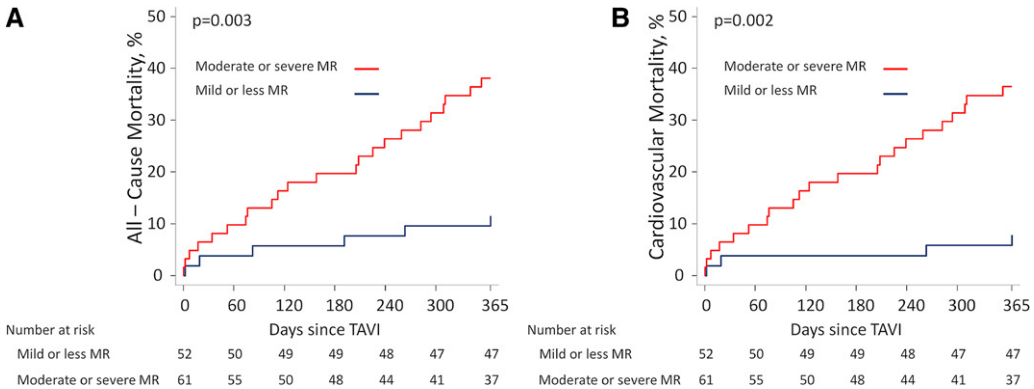

Figure 1. Kaplan–Meier analysis of death (**A**) and cardiovascular death (**B**) at 1 year among patients with low-ejection fraction, low-gradient severe aortic stenosis undergoing transcatheter aortic valve implantation (TAVI) stratified according to the presence of mild or less mitral regurgitation (MR) and moderate or severe MR at baseline.

Table 5. Unadjusted and Adjusted Clinical Outcomes at 1 Year of Transcatheter Aortic Valve Implantation Patients Stratified According to MR Grade

	Mild or Less MR	Moderate or Severe MR	Unadjusted Events		Adjusted Events	
	n=52	n=61	HR or RR (95% CI)	*P* Value	HR or RR (95% CI)	*P* Value
1-y follow-up						
All cause death, n (%)	6 (11.5)	23 (38.1)	3.85 (1.57–9.47)	0.003	3.27 (1.31–8.15)	0.011
Cardiovascular death, n (%)	4 (7.9)	22 (36.5)	5.50 (1.89–15.97)	0.002	4.62 (1.57–13.60)	0.005
Cerebrovascular events	3 (5.8)	4 (6.7)	1.18 (0.26–5.26)	0.83	0.78 (0.16–3.81)	0.76
Major stroke, n (%)	2 (3.9)	2 (3.4)	0.88 (0.12–6.25)	0.90	0.27 (0.02–3.08)	0.29
Myocardial infarction, n (%)	1 (1.9)	1 (1.7)	0.85 (0.05–13.61)	0.91	0.37 (0.02–8.06)	0.53
All cause death or major stroke, n (%)	7 (13.5)	25 (41.4)	3.61 (1.56–8.36)	0.003	2.86 (1.21–6.76)	0.016
All cause death, major stroke, or MI, n (%)	7 (13.5)	25 (41.4)	3.62 (1.56–8.38)	0.003	2.88 (1.22–6.81)	0.016

Depicted are counts (incidence rates % from life-tables estimate). HRs (95% CI) from Cox Regressions for time-to-event data. In case of zero events continuity correct RR (95% CI) with Fisher test *P* values are reported. Adjusted HRs (95% CI) from Cox Regressions, correcting for peripheral vascular disease and logistic Euroscore. CI indicates confidence interval; HR, hazard ratios; MR, mitral regurgitation; and RR, risk ratios.

area, mean gradient, LVEF, or right ventricular ejection fraction were observed. TAVI patients with moderate to severe MR had significantly worse diastolic function as compared with mild or less MR TAVI patients. Among TAVI patients with moderate to severe MR, MR was classified as functional in 44 of 61 (72%) and degenerative in 17 of 61 (28%).

Contractile reserve was present in 11 of 17 (64.7%) of mild or less MR TAVI patients and 16 of 19 (84.2%) of TAVI patients with moderate or severe MR (*P*=0.18). Baseline mean gradient was significantly lower among the moderate to severe MR group (23.4±6.2 mm Hg versus 18.7±7.1 mm Hg; *P*=0.049) but mean gradients reached at peak dobutamine infusion were similar (37.2±7.3 mm Hg versus 32.0±10.7 mm Hg; *P*=0.10). Aortic valve area remained fixed at peak dobutamine infusion in patients with both mild or less MR (aortic valve area baseline versus peak dobutamine infusion: 0.78±0.28 mm Hg versus 0.81±0.34 mm Hg) and moderate or severe MR (0.80±0.23 mm Hg versus 0.83±0.25 mm Hg).

As compared with LEF-LG patients assigned to MT, patients assigned to TAVI had a higher baseline LVEF (29.3±9.6% versus 34.4±11.2%; *P*=0.014; Table II in the Data Supplement).

Baseline Invasive Hemodynamic Characteristics

Invasive hemodynamic characteristics of TAVI patients stratified according to MR severity are presented in Table 3. As compared with mild or less MR TAVI patients, moderate or severe MR TAVI patients had significantly higher valvular resistances and valvuloarterial impedances. In addition, moderate or severe MR TAVI patients had significantly higher pulmonary artery pressures (mean and systolic) and a higher incidence of pulmonary hypertension as compared with mild or less MR patients. Pulmonary hypertension was predominantly postcapillary in both the TAVI groups. TAVI patients with moderate to severe MR had a significantly lower stroke volume and cardiac output as compared with TAVI patients with mild or less MR.

As compared with LEF-LG patients assigned to MT, patients undergoing TAVI had somewhat higher stroke volume indices (21.0±5.1 mL/m^2 versus 24.5±7.2 mL/m^2; *P*=0.021) and lower heart rates (86.8±12.2 bpm versus 79.7±16.4 bpm; *P*=0.041; Table III in the Data Supplement).

Procedural Characteristics

Procedural characteristics of TAVI patients are given in Table 4. Mean procedural time was 66±38 minutes. Most

Table 6. Clinical Outcomes of Patients With Low-Ejection Fraction, Low-Gradient Severe Aortic Stenosis Assigned to TAVI Versus Medical Therapy Stratified According to MR Grade

	Medical		TAVI		Mild or Less MR Medical vs TAVI		Moderate or Severe MR Medical vs TAVI	
	Mild or Less MR	Moderate or Severe MR	Mild or Less MR	Moderate or Severe MR	HR or RR (95% CI)	*P* Value	HR or RR (95% CI)	*P* Value
	n=19	n=20	n=52	n=61				
1-y follow-up								
All-cause death, n (%)	11 (57.9)	13 (65.7)	6 (11.5)	23 (38.1)	0.14 (0.05–0.38)	<0.001	0.38 (0.19–0.75)	0.005
Cardiovascular death, n (%)	10 (55.4)	13 (65.7)	4 (7.9)	22 (36.5)	0.10 (0.03–0.33)	<0.001	0.36 (0.18–0.73)	0.004

Depicted are counts (incidence rates % from life-tables estimate). HRs (95% CI) from Cox Regressions for time-to-event data. CI indicates confidence interval; HR, hazard ratios; MR, mitral regurgitation; RR, risk ratios; and TAVI, transcatheter aortic valve implantation.

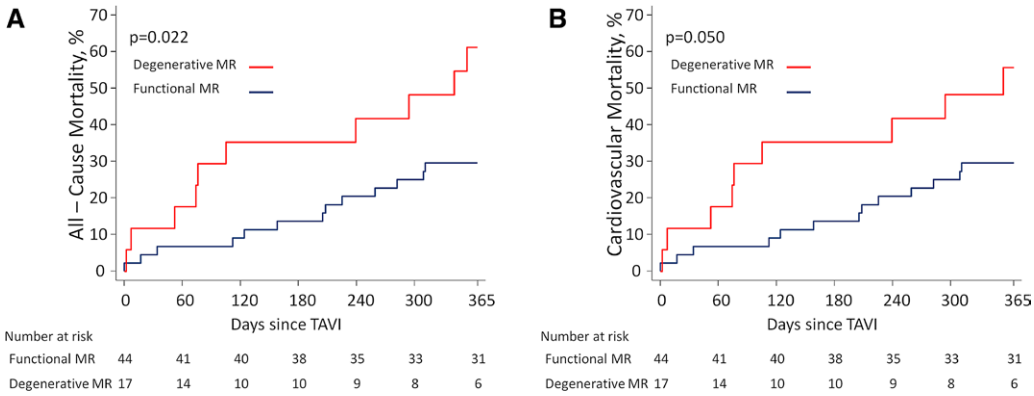

Figure 2. Kaplan–Meier analysis of death (**A**) and cardiovascular death (**B**) at 1 year among patients undergoing transcatheter aortic valve implantation (TAVI) with moderate or severe mitral regurgitation (MR) only stratified according to MR cause (functional vs degenerative).

patients underwent transfemoral TAVI under conscious sedation. Mean length of hospital stay was 7.9±5.6 days. One patient with moderate MR undergoing transapical TAVI required conversion to conventional SAVR and subsequently died. Overall, 16.8% of patients had postprocedural ≥moderate aortic regurgitation with no significant differences between groups (*P*=0.37).

Clinical Outcomes of TAVI Patients Stratified According to MR Grade

One-year follow-up was complete for 112 of 113 (99.1%) TAVI patients with 1 patient withdrawing consent for follow-up 113 days after TAVI. Event rates with crude and adjusted hazard ratios (adj HR) for all major clinical end points at 30 days and 12 months are provided in Table IV in the Data Supplement and Table 5, respectively.

Six deaths occurred at 30 days of which 4 were in-hospital. No significant differences in all-cause mortality (3.8% versus 6.6%; *P*=0.52), cardiovascular death (3.8% versus 6.6%; *P*=0.52), or major adverse cardiovascular and cerebrovascular events (3.8% versus 11.5%; *P*=0.17) were observed at 30 days between groups. There were no significant differences in other end points at 30 days (Table IV in the Data Supplement).

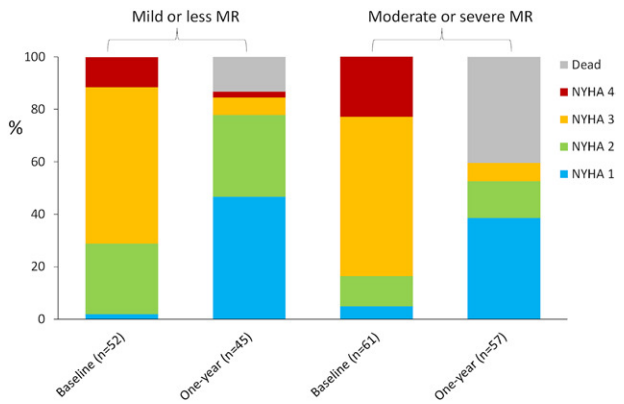

Figure 3. Functional status expressed by the New York Heart Association (NYHA) classification at baseline and 1-year follow-up among low-ejection fraction, low-gradient, severe aortic stenosis patients undergoing transcatheter aortic valve implantation stratified according to the presence of mild or less mitral regurgitation (MR) and moderate or severe MR at baseline.

Time-to-event curves for all-cause mortality and cardiovascular death among all TAVI patients are shown in Figure 1. As compared with TAVI patients with mild or less MR, LEF-LG TAVI patients with moderate to severe MR had incidence higher rate of all-cause mortality (11.5% versus 38.1%; unadjusted HR, 3.85; 95% CI, 1.57–9.47; *P*=0.003), which was driven by cardiovascular death (7.9% versus 36.5%; unadjusted HR, 5.50; 95% CI, 1.89–15.97; *P*=0.002; Table 6). On multivariate analysis, moderate or severe MR was an independent predictor for all-cause mortality (adj HR, 3.27; 95% CI, 1.31–8.15; *P*=0.011), cardiac death (adj HR, 4.62; 95% CI, 1.57–13.60; *P*=0.005) and major adverse cardiovascular and cerebrovascular events (adj HR, 2.88; 95% CI, 1.22–6.81; *P*=0.002) at 1 year among TAVI patients after adjusting for the univariate predictors of peripheral vascular disease and logistic EuroSCORE. Time-to-event curves stratified according to MR cause (ie, functional versus degenerative) among moderate or severe MR TAVI patients only are shown in Figure 2. As compared with functional MR, patients with degenerative MR had a higher rate of death (29.5% versus 61.2%; adj HR, 3.38; 95% CI, 1.32–8.67; *P*=0.011) driven by cardiac death (adj HR, 2.92; *P*=0.029) at 1 year.

NYHA functional class at baseline and 1-year follow-up in both the TAVI groups is shown in Figure 3. At 1 year, 58 (56.9%) patients improved, 12 (11.8%) patients had no change, 3 (2.9%) had worsened, and 29 (28.4%) had died (χ^2 test, *P*=0.02). Improvement in NYHA class of the surviving patients did not differ between moderate or severe MR (82%) as compared with surviving patients with mild or less MR (76%; Fisher test, *P*=0.77).

Clinical Outcomes of Patients Assigned to TAVI Versus MT Stratified According to MR Grade

Event rates with crude HRs for all-cause mortality and cardiovascular death at 1-year comparing patients undergoing TAVI versus patients assigned to MT stratified according to MR grade (mild or less MR versus moderate or severe MR) are shown in Table 6. Time-to-event curves for all-cause mortality and cardiovascular death among all patients are shown in Figure 4. As compared with patients with mild or less MR undergoing MT, patients with mild or less MR undergoing TAVI had a significantly lower all-cause (HR, 0.14; 95% CI, 0.05–0.38; *P*<0.001) and cardiovascular mortality (HR, 0.10;

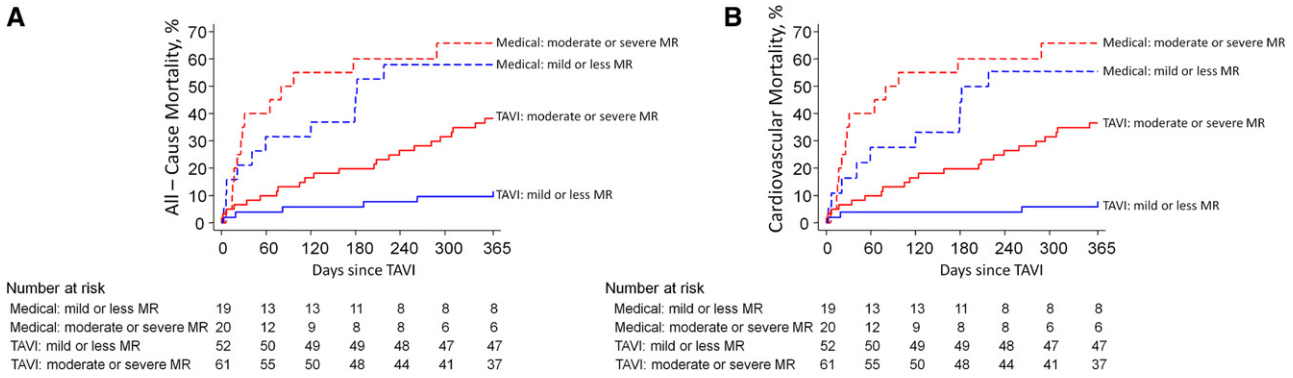

Figure 4. Kaplan–Meier analysis of death (**A**) and cardiovascular death (**B**) at 1 year among patients with low-ejection fraction, low-gradient severe aortic stenosis assigned to medical therapy vs transcatheter aortic valve implantation (TAVI) stratified according to the presence of mild or less mitral regurgitation (MR) and moderate or severe MR at baseline.

95% CI, 0.03–0.33; $P<0.001$). As compared with patients with moderate or severe MR undergoing MT, patients with moderate or severe MR undergoing TAVI had a significantly lower all-cause (HR, 0.38; 95% CI, 0.019–0.75; $P=0.005$) and cardiovascular (HR, 0.36; 95% CI, 0.18–0.73; $P=0.004$) mortality at 1 year.

Echocardiographic Outcomes Among TAVI Patients

Changes in MR at baseline, discharge, and 1 year are shown in Figure 5. Among moderate to severe MR patients surviving to discharge, an acute improvement in MR was observed in 28 (46.7%) patients, no change in 25 (41.7%) and worsened in 4 (6.7%). Twelve patients with mild MR at baseline progressed to moderate MR after TAVI (Figure 4). No significant differences in overall 1 year survival rates were observed between patients with no change or worsening MR and patients with improvement of MR on discharge echo (Figure in the Data Supplement).

One-year echocardiographic follow-up was performed a median of 379 days (IQR, 262–511 days) after TAVI and was available in 77 of 84 (92%) surviving patients (Figure 6). Among moderate to severe MR patients, 19 (31.7%) patients improved, 16 (26.7%) patients had no change, 2 (3.3%) patients worsened an MR grade, and 23 (38.3%) patients had died at 1-year follow-up. Among mild or less MR patients, 6 (13.0%) patients had moderate MR at 1-year follow-up, of whom 4 were observed to have had moderate MR at discharge.

Changes in LVEF, left ventricular end-systolic diameter and pulmonary artery systolic pressure among 1-year survivors are shown in Figure 7. Both LVEF and pulmonary artery systolic pressure significantly improved at 1-year with no significant interaction between groups. A borderline trend toward a significant reduction in left ventricular end-systolic diameter ($P=0.08$) was observed at 1-year with no significant interaction between groups. No overall significant changes in LVEDD ($P=0.29$) or LV mass indices ($P=0.91$) were observed at 1-year and no significant interaction was observed between groups for either variables.

As compared with 1-year survivors who underwent TAVI, nonsurvivors who underwent TAVI at 1 year had significantly worse LVEF, significantly larger left atrial diameters and a significantly higher prevalence of moderate to severe MR (Table V in the Data Supplement).

Discussion

To the best of our knowledge, this study is the first to assess the effect of MR on clinical outcomes among patients with LEF-LG severe AS undergoing TAVI. Our main finding was that moderate or severe MR was a strong independent predictor of 1-year mortality among patients with LEF-LG severe AS undergoing TAVI, which was predominantly driven by cardiac death. Among moderate or severe MR patients undergoing TAVI, degenerative MR was associated with worse outcomes as compared with functional MR patients. We also observed that LEF-LG patients assigned

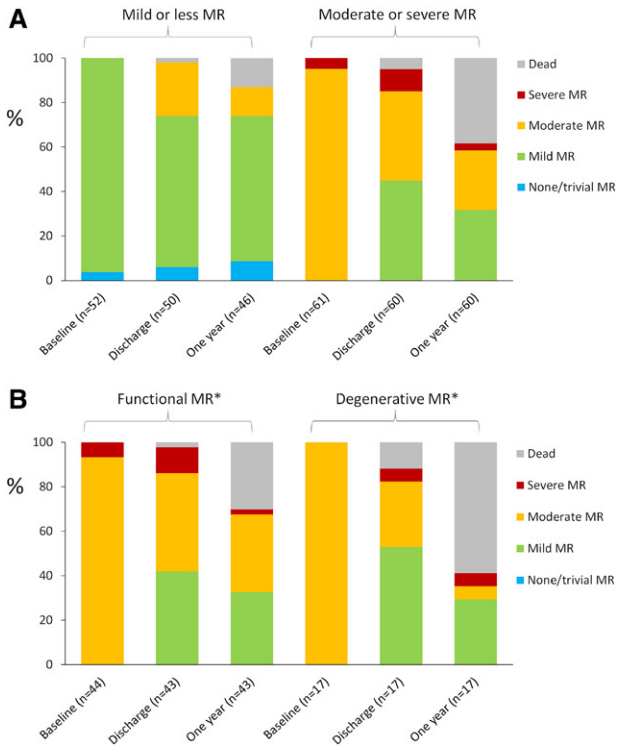

Figure 5. Changes in mitral regurgitation (MR) over time (baseline, discharge, and 1 year) among patients with low-ejection fraction, low-gradient (LEF-LG) severe aortic stenosis undergoing transcatheter aortic valve implantation stratified according to presence of mild or less MR and moderate or severe MR at baseline (**A**) and according to functional versus degenerative cause among LEF-LG patients with moderate to severe MR at baseline (**B**).

to MT had a dismal prognosis, independent of MR severity grade, suggesting that TAVI should not be withheld from symptomatic patients with LEF-LG severe AS even in the presence of moderate to severe MR. However, the latter observation should be considered hypothesis generating owing to the fact that the MT group sample size was relatively small and that patients assigned to MT were at higher surgical risk as compared with TAVI patients. Among TAVI patients, the majority of deaths occurred in the late period (>30 days) with no differences observed at 30 days. However, it should be noted that there were not enough events in the early period (<30 days) to test for a mortality difference at this stage. Immediately after TAVI, an improvement in MR grade was observed in almost half of the patients with moderate to severe MR at baseline. However, MR improvement did not predict 1-year survival. Among surviving patients with moderate MR at 1-year (all patients with severe MR died), improvements in NYHA functional class status was associated with improvement in LVEF and pulmonary pressures although LV remodeling was limited in both the groups. Just under a third of patients (31%) with moderate or severe MR at baseline demonstrated an improvement in MR severity 1 year after TAVI.

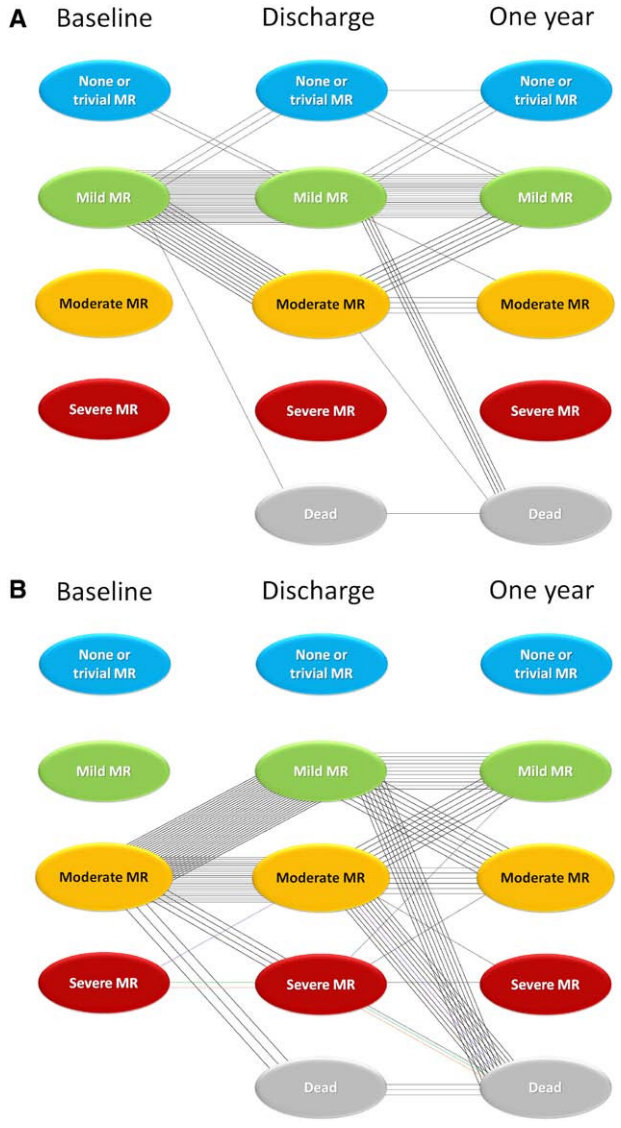

Figure 6. Tracked outcomes of individual patients with low-ejection fraction, low-gradient severe aortic stenosis undergoing transcatheter aortic valve implantation over time (baseline, discharge, and 1 year) according to mitral regurgitation (MR) grade or death at follow-up, stratified according to mild or less MR (**A**) or moderate or severe MR (**B**). Two patients (1 in each group) were missing discharge echocardiograms and 7 patients were missing 1-year follow-up echocardiograms (6 in mild or less MR group and 1 in moderate or severe MR group). Baseline to discharge: $P<0.001$; of survivors at discharge: $P<0.001$. Discharge to 1-year follow-up $P=0.006$; of survivors at 1 year: $P=0.11$.

Moderate to Severe MR in Unselected TAVI Candidates

Previous studies have shown that moderate to severe MR is present in up to one fifth of unselected patients undergoing TAVI.[19–22] However, the effect of moderate or severe MR on clinical outcomes among an unselected patient population undergoing TAVI is controversial.[23–25] In contrast to this study, most studies to date have been confounded by the fact that MR groups have been unevenly matched with moderate or severe MR patients undergoing TAVI having significantly higher baseline risk scores, poorer LV function and a higher prevalence of atrial fibrillation and pulmonary hypertension

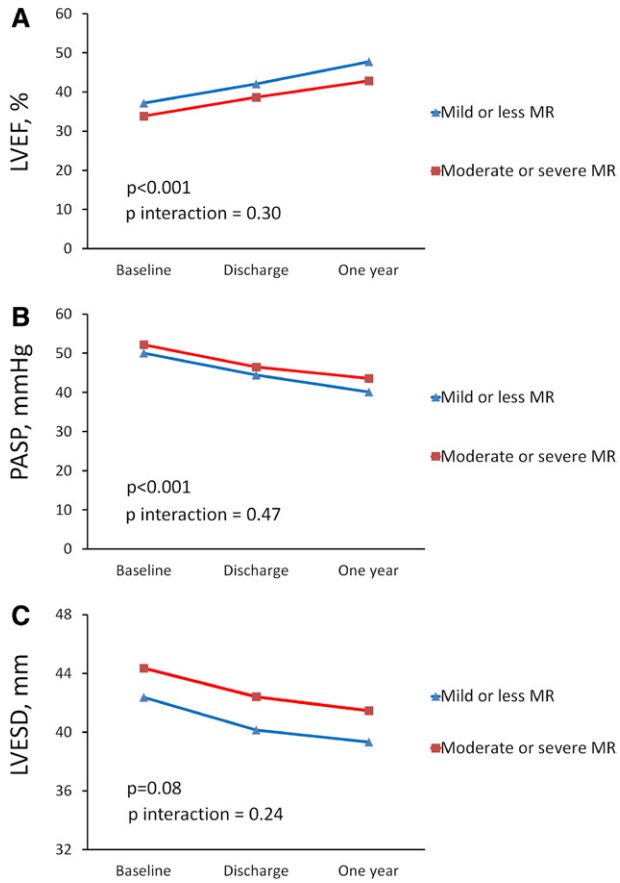

Figure 7. Changes in left ventricular ejection fraction (LVEF; **A**), pulmonary artery systolic pressure (PASP; **B**) and left ventricular end-systolic diameter (LVESD; C) over time (baseline, discharge, and 1-year) among patients with low-ejection fraction, low-gradient severe aortic stenosis undergoing transcatheter aortic valve implantation stratified according to mild or less mitral regurgitation (MR) and moderate or severe MR.

as compared with patients with mild or less MR.[23–25] Toggweiler et al[24] reported that moderate to severe MR was associated with a higher 30 days, but not late, mortality among unselected patients undergoing TAVI with a balloon expandable valves. They also found that improvement in MR was predicted by high gradients, functional MR, absence of pulmonary hypertension, and absence of atrial fibrillation. In the Placement of Aortic Transcatheter Valves (PARTNER) A trial, Barbanti et al[23] reported no significant differences in overall 2-year mortality among patients with moderate to severe MR undergoing TAVI as compared with patients with mild or less MR. Conversely, moderate or severe MR at baseline was associated with a significantly higher 2-year mortality rate among SAVR patients.[23] A study from a large (n=1007) multicentre Italian registry reported that moderate and severe MR was associated with significantly higher mortality rates both at 30 days and 1 year as compared with mild or less MR in patients undergoing TAVI with a self-expanding device.[25] However, both the moderate and the severe MR groups had significantly higher baseline risk scores, higher pulmonary pressures, and a prevalence of atrial fibrillation as compared with mild or less MR groups.[25]

MR in Patients With Low-Ejection Fraction, Low-Gradient Severe AS Undergoing TAVI

In most studies to date, the prevalence of moderate or severe MR is higher among patients with LEF-LG as compared with high-gradient severe AS patients (Figure 8). LEF-LG patients have dilated LV cavities, which can lead to annular dilatation and reduce or eliminate normal coaptation between the anterior and the posterior mitral valve leaflets resulting in MR.[33] Most patients had dilated LV cavities in this study (Table 2).

We observed that LEF-LG patients with moderate or severe MR undergoing TAVI had a markedly higher 1-year mortality rates as compared with similar patients presenting with mild or less MR after TAVI. Furthermore, mortality was 3 times higher with degenerative as compared with functional MR among moderate or severe MR TAVI patients. The data shown in Figure 3 might be interpreted as showing that TAVI in LEF-LG patients with moderate or severe MR is a high risk/reward proposition. It seems that most patients are either dead or greatly improved at 1 year after the procedure. The data shown in Figure 6 show the dynamic nature of MR after TAVI. The reason why MR changes between the early and late time points may relate to the cause of MR. Whereas functional MR may be expected to improve over time after TAVI, degenerative MR would not since the primary pathology is because of intrinsic abnormalities of the mitral valve apparatus.[33] The reasons for the observed higher mortality rate with significant MR are unclear. MR is a known cause of pulmonary hypertension, which is an independent predictor of mortality after TAVI.[20] Pulmonary artery pressures were significantly higher among moderate or severe MR patients on right heart catheterization. Furthermore, pulmonary hypertension was predominantly postcapillary suggesting a left heart cause. The added burden of moderate or severe MR may lead to a worse severity of PH, which may translate into the higher mortality rates observed. An alternative hypothesis may relate to the fact that patients with moderate or severe MR may have a more severe underlying myocardial disease resulting in lower contractile reserve, which may be multifactorial such as an end-stage manifestation of AS or influence of other factors, such as arterial hypertension, aging, and fibrosis. It is also possible that moderate or severe MR may reduce forward stroke volume and, thereby contribute to pseudostenosis and thus patients who undergo TAVI may not experience as much of a benefit from TAVI. However, this would not be expected to account for the higher mortality observed in the moderate to severe MR group.

Clinical Implications

This study has clinical implications about patient selection and the management of patients presenting with LEF-LG severe AS. First, TAVI can be safely performed in LEF-LG patients regardless of MR severity because no differences periprocedural or 30-day outcomes were observed. However, because of the poor medium term outlook among LEF-LG patients with even moderate MR, the question remains as to whether it should be done on everybody. Although overall and cardiac mortality rates observed among LEF-LG patients with moderate or severe MR in this study (38.1% and 36.5%, respectively) were lower than that observed in the medical cohort of the PARTNER B trial (49.7% and 41.9%, respectively), this study does raise questions about futility in this patient subset.[22] However, we observed that LEF-LG patients with moderate or severe MR assigned to MT during the same treatment period at

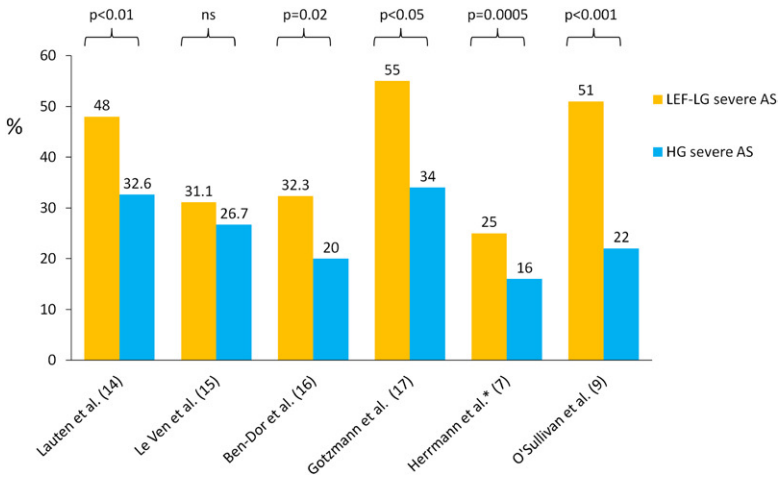

Figure 8. Comparison of the prevalence of moderate or severe mitral regurgitation between patients with low-ejection fraction, low-gradient (LEF-LG) and high-gradient (HG) severe aortic stenosis in studies assessing patients undergoing transcatheter aortic valve implantation. *In Herrmann et al,[7] the comparison was between low-flow and normal flow only irrespective of the mean gradient or left ventricular ejection fraction.

our institution had significantly worse outcomes as compared with LEF-LG patients with moderate or severe MR assigned to TAVI (Figure 4; Table 6). These results suggest that it is not futile to treat patients with LEF-LG severe AS and concomitant moderate or severe MR with TAVI. With the advent of novel percutaneous methods for the treatment of MR in high-risk patients (eg, MitraClip), it remains to be seen whether such procedures combined with TAVI may improve clinical outcomes among LEF-LG patients with moderate or severe MR.[34]

Limitations

First, this is a single-center observational study and may contain bias. However, our best knowledge, this is the first study to report the effect of moderate to severe MR on clinical outcomes among patients with LEF-LG undergoing TAVI. Data were prospectively collected and all events were independently adjudicated by a clinical events committee. Second, this was a selective patient population and, therefore, the number of patients included in the study was relatively small. However, our numbers favorably compare with previous studies focusing on LEF-LG and SAVR and TAVI.[10,14,15] Third, dobutamine stress echocardiography was only performed on a third of patients undergoing TAVI included in this study. Fourth, given that there were more deaths in the moderate to severe MR among TAVI patients, the results of the analyses on the echocardiographic parameters baseline, discharge, and at 1 year among TAVI patients are affected by this. Because the deaths could be interpreted as cases of missing data, their exclusion can affect the results of the analyses, especially because these observations are not missing at random. This could, therefore, introduce an unmeasured bias. Finally, the sample size of the MT control group was relatively small and precluded propensity score or inverse probability treatment weighting analysis between MT and TAVI groups. In addition, MT patients were higher risk as compared with TAVI patients.

Conclusions

Moderate or severe MR is a strong independent predictor of 1-year mortality among patients with LEF-LG undergoing TAVI. Degenerative MR predicts a worse outcome among moderate or severe MR patients. LEF-LG patients assigned to MT have a dismal prognosis independent of MR severity suggesting that TAVI should not be withheld from patients with LEF-LG severe AS even in the presence of concomitant moderate or severe MR.

Disclosures

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